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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
~~ULM, J~~

18N2/0330

PATENT ADMINISTRATOR
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ART UNIT	PAPER NUMBER
1812	24

DATE MAILED: 03/30/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ ~~This~~ application has been examined ☒ ~~Responsive~~ to communication filed on 12/17/93 ☒ ~~This~~ action is ~~made~~ final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ ~~Notice~~ of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ ~~Claims~~ 42 to 65 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ ~~Claims~~ 22 to 38 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ ~~Claims~~ 42 to 68 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not accepteble (see explenation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Newly submitted claims 47 to 68 are pending in the instant application. Claims 27 through 38 have been canceled as requested by Applicant in Paper Number 23.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the production of any and all fusion proteins in which a proteolytic cleavage site present in a target protein is cleaved at a rate less than an analogous site at the junction of the fusion protein. To illustrate this point Applicant is requested to consider a target protein containing a methionine residue followed by other than a cysteine residue. Fusion proteins are commonly joined by a methionine residue to permit subsequent cleavage by cyanogen bromide. Because cyanogen bromide cleavage of proteins is not generally sterically hindered by protein structure, artisans do not generally use this configuration to produce proteins containing methionine residues. The instant specification does not provide the guidance needed to produce a

fusion protein containing two cyanogen bromide cleavage sites in which one is preferentially cleaved over the other. Whereas the incorporation of a flexible linker into the junction of a fusion protein would clearly be expected to enhance the accessibility of an adjacent enzymatic cleavage site, such a configuration would not appear to have a comparable effect upon a chemical cleavage site. Additionally, if an artisan constructs a fusion protein according to the instant invention and the junction cleavage site is not preferentially cleaved over a target protein site, the instant specification does not provide the needed guidance to correct the problem. In effect, an artisan would have to resort to repeated trial and error to produce such a protein and this would constitute undue experimentation.

Claim 62 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 54 and 55 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. The limitations of these claims are recited virtually verbatim in claim 47, from which they depend. Claim 54, for example, limits the fusion protein of claim 47 to one containing at least one amino acid defining a cleavage site. Lines five and six of claim 47 have already imposed this limitation upon the claimed protein.

Claims 47 to 68 are rejected under 35 U.S.C. § 103 as being unpatentable over the Cousens et.al. patent (1A, of record) in

view of the Cohen et.al. patent (1B, of record) essentially for those reasons of record as applied to claims 27 to 38 in Paper Numbers 16 and 21.

Applicant's allegation that the Cousens et.al. patent does not receive benefit of the filing date of parent application Serial Number 06/717,209 under 35 U.S.C. § 120 is incorrect. Applicant's position that this priority application can not be relied upon if it was not enabling for a subsequently patented invention is not disputed. The Cousens et.al. patent, however, is clearly entitled to receive benefit for that material which is common to both applications and which was enabling for subsequently allowed claims. The working examples of fusion proteins which are common to both of these applications have been relied upon for the pending rejections and these examples, as presented in application Serial Number 06/717,209 and without the benefit the additional material provided by the continuing application on which this patent issued, were clearly enabling for claims 12 to 15, 17 and 18 of that issued patent. There is no question, therefore, that the Cousens et.al. patent should be given benefit of the filing date of parent application Serial Number 06/717,209 as indicated in M.P.E.P. 901.02 for that material which is common to both.

Applicant has requested factual evidence that one of ordinary skill would have known that stearic hinderance was a factor to be considered in designing a fusion protein cleavage

site at the time that Cousens et.al. constructed their invention. The Löfdahl et.al. publication is being provided because it shows that this problem had been recognized and was well known in the art prior to the making of the invention of Cousens et.al. The text from line 2 of page 6 to the bottom of page 7 of the Löfdahl et.al. publication summarizes the state of the art of fusion protein cleavage prior to the Cousens et.al. invention. This reference explicitly taught that "[o]ften it may be preferred to use chemical cleaving agents [to cleave fusion proteins] because protease recognition sequences may be sterically hindered in the produced fused protein." This reference also stated that "[t]he techniques for introducing the corresponding DNA sequences coding for such cleavage susceptible peptide units or residues into the DNA sequence coding for the fused protein or polypeptide are well-known per se in the art and need not be discussed in any detail herein". This reference clearly shows that an artisan such as Cousens et.al. was well aware that a protease cleavage site could be sterically unavailable in a fusion protein whereas a chemical cleavage site generally was not.

As shown by the table on page 15 of the Cousens et.al. priority document, the construction of five fusion proteins was described therein. Three of these proteins contained chemical cleavage sites and two contained protease cleavage sites. Only the two proteins containing protease cleavage sites also contained serine-threonine linkers directly adjacent to these

sites. For Applicant to conclude that these linkers were not included to facilitate cleavage of these proteins by relieving steric hinderance at the cleavage site requires one to ignore the context in which they were made both relative to the other three proteins described therein and in relation to a knowledge of the contemporary art of fusion protein cleavage as exemplified here by the Löfdahl et.al. publication. Such a conclusion is clearly improper.

Applicant has alleged that there is no factual basis for concluding that an artisan of ordinary skill in protein chemistry, and Cousens et.al. specifically, would have recognized that the serine-threonine-serine-threonine-serine- and serine-threonine-serine- linkers described in the Cousens et.al. priority document were flexible. Included with this action is an excerpt from an undergraduate biochemistry textbook which was originally published in 1970 (A. L. LEHNINGER, "BIOCHEMISTRY" published 1978 (fourth printing) by Worth Publishers, Inc. (N.Y.), pages 130 and 131). This excerpt teaches that the amino acids tyrosine, cysteine, asparagine, serine, isoleucine, threonine, glutamic acid, aspartic acid, lysine, arginine and glycine are helix-destabilizing amino acids and that a polypeptide composed exclusively of one or more of these amino acids would be expected to have a random form in which the flexible backbone undergoes continuous change as the result of thermal motion. Unless one accepts the premise that Cousens

et.al. was completely ignorant of basic protein chemistry, one has to conclude that Cousens et.al. was well aware that the serine-threonine linkers they constructed de novo were flexible and would facilitate the cleavage of an adjacent protease cleavage site by alleviating any potential steric hinderance in a fusion protein. There is no other credible explanation for the construction and use of these linkers in this capacity.

Applicant has further alleged that the linkers described by Cousens et.al. do not inherently possess the characteristics of being flexible and facilitating cleavage. In this case, inherency is a question of fact that can be determine using contemporary as well as prior art. These linkers clearly meet the structural requirements for both flexibility and cleavability as indicated by the text on lines 16 to 47 of the issued Cousens et.al. patent and the text in the last paragraph spanning pages 6 and 7 of the instant specification. Applicant has argued that one can not be certain of these characteristics because the art of protein chemistry is allegedly unpredictable. Applicant is advised that, if the art is as unpredictable as they have suggested, then the instant specification is only enabled for those working examples disclosed therein because it clearly fails to provide a predictive element which was not present in the prior art. The evidence that the serine-threonine linkers described in the working examples of the Cousens et.al. priority document can reasonable be expected to be both flexible and

selectively cleavable can be found in the facts of record in the instant application and art of record and Applicant has not provided a single showing of fact or reasoned argument which contradicts either this evidence or the conclusion drawn from it. If Applicant has evidence that a proinsulin::yeast pyruvate kinase fusion protein which has been joined by a lysine-arginine-serine-threonine-serine linker is not cleaved by trypsin more readily than one which has been joined only by a lysine-arginine linker or that a proinsulin::superoxide dismutase fusion protein which has been joined by a lysine-arginine-serine-threonine-serine-threonine-serine linker is not cleaved by trypsin more efficiently than one which has been joined only by a lysine-arginine linker, they are encouraged to make it of record.

It is clear that Cousens et.al. was not only aware of the steric hinderance problem which is addressed by the instant invention and which was well known in the art of fusion protein construction prior to the making of their invention but also was aware of the solution which is Applicant's invention. Cousens et.al. described a fusion protein having a selectively cleavable site between its two components and, where that site was to be enzymatically cleaved, described the incorporation of a flexible linker adjacent to that site to facilitate such cleavage.

The Cohen et.al. patent has been relied upon because it shows that the avoidance of cysteine residues in the linker and leader peptide of a fusion protein to prevent the covalent

interaction of these components with the desired protein was old and well known in the art at the time of the instant invention. Applicant has not shown this to be in error.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to John D. Ulm at telephone number (703) 308-4008.

GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT ~~188~~ 1812